Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-090-z Selpercatinib

Stand: Mai 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Selpercatinib
[zur Behandlung von Erwachsenen mit fortgeschrittenen oder metastasierten RET-Fusions-positiven Tumoren]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Arzneimittel zur Behandlung des Schilddrüsenkarzinoms oder des nicht-kleinzelligen Lungenkarzinoms werden nicht berücksichtigt. Es gibt keine weiteren explizit zur Behandlung von RET-Fusions-positiven Tumoren zugelassenen Arzneimittel. Angesichts des vorliegenden Tumor-agnostischen Anwendungsgebietes erscheint eine Recherche und Information über sämtliche zur Behandlung von soliden Tumoren zugelassenen Arzneimittel und weiteren Behandlungsoptionen nicht sinnvoll. Es wurde eine orientierende Literaturrecherche in Bezug auf den Biomarker durchgeführt.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-090-z (Selpercatinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	2. Mai 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis 3
1 Indikation 4
2 Systematische Recherche 4
3 Ergebnisse 5
3.1 Cochrane Reviews 5
3.2 Systematische Reviews 5
3.3 Leitlinien 5
4 Detaillierte Darstellung der Recherchestrategie 19
Referenzen 22

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AHS	Alberta Health Services
AE	Adverse events
ASCO	American Society of Clinical Oncology
dMMR	Mismatch repair deficient
ECRI	Emergency Care Research Institute
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IHC	Immunohistochemistry
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI/CI	Konfidenzintervall
LoE	Level of Evidence
MSI-H	Microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small-cell lung cancer
OR	Odds Ratio
PFS	Progression free survival
PS	Performance status
RR	Relatives Risiko
SBRT	Stereotactic body radiation therapy
SIGN	Scottish Intercollegiate Guidelines Network
TMB-H	Tumor mutational burden-high
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Patienten und Patientinnen mit fortgeschrittenen oder metastasierten RET-Fusions-positiven Tumoren (exklusive NSCLC oder Schilddrüsenkarzinom).

Hinweis zur Synopse: Die Recherche und Synopse der Evidenz wurden aufgrund der histologieunabhängigen, tumorangnostischen Indikation erweitert. Entsprechend wurde eine zusätzliche orientierende Recherche durchgeführt, um jene Tumore festzuhalten, welche die höchste Prävalenz der RET-Fusionen aufweisen. Diese sind (exklusive NSCLC oder Schilddrüsenkarzinom): Ovarialkarzinom, Pankreaskarzinom, Kolorektalkarzinom, Mammakarzinom, Speicheldrüsenkarzinom, Neuroendokrine Tumore sowie Krebserkrankung mit unbekanntem Primärtumor [1,8].

Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation RET-Fusions-positive Tumore durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt. Zusätzlich erfolgte eine iterative Suche nach Leitlinien auf den Internetseiten von Leitlinienorganisationen nach den Indikationen Ovarialkarzinom, Pankreaskarzinom, Kolorektalkarzinom, Mammakarzinom, Speicheldrüsenkarzinom, Neuroendokrine Tumore sowie Krebserkrankung mit unbekanntem Primärtumor.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 23.04.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 841 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.3 Leitlinien

National Comprehensive Cancer Network (NCCN), 2023 [4].

Neuroendocrine and Adrenal Tumors

Zielsetzung/Fragestellung

These guidelines discuss the diagnosis and management of both sporadic and hereditary neuroendocrine and adrenal tumors and are intended to assist with clinical decision-making. Most of the guideline sections pertain to well-differentiated, low- to intermediate-grade tumors, although well differentiated high-grade tumors and poorly differentiated/ large or small cell carcinomas are also addressed.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz wird die LL jedoch ergänzend dargestellt.

<u>Grundlage der Leitlinie</u>

Version 1.2023 der Leitlinie, Erstveröffentlichung unklar.

- Repräsentatives Gremium mit Patientenvertretung;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt (NCCN Guidelines Panel Disclosures);
- Systematische Suche wird erwähnt, jedoch keine detaillierte Beschreibung und Suchzeitraum, keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren sind nicht näher beschrieben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist zudem über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

<u>Recherche/Suchzeitraum:</u>

- Es wurde kein Suchzeitraum für die Literaturrecherche angegeben
- PubMed database

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet ('Discussion update in progress').

Empfehlungen

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Extrapulmonary Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell Carcinoma/ Mixed Neuroendocrine–Non-Neuroendocrine Neoplasm

Extrapulmonary Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell Carcinoma/Mixed Neuroendocrine–Non-Neuroendocrine Neoplasm		
Resectable disease	**Locoregional unresectable disease: Chemoradiation (concurrent/sequential)**	**Locoregional unresectable/metastatic disease: Systemic therapy[o]**
• Carboplatin + etoposide[27] • Cisplatin + etoposide[13] • FOLFIRI • FOLFOX • Temozolomide ± capecitabine	• Capecitabine (when etoposide + platinum is not feasible) • Carboplatin + etoposide • Cisplatin + etoposide	**Chemotherapy:** • Carboplatin + etoposide[27] • Cisplatin + etoposide[13] • Carboplatin + irinotecan • Cisplatin + irinotecan • FOLFIRI • FOLFIRINOX[28,29,30] • FOLFOX • Temozolomide ± capecitabine **Immunotherapy:** • Pembrolizumab[m] (if MSI-H, dMMR, or TMB-H tumors [≥10 mut/Mb]) • Nivolumab + ipilimumab[25,26,31,32] (category 2B) (only for metastatic disease with progression) **Targeted Therapy:** • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[p,33] • Entrectinib (if *NTRK* gene fusion-positive)[q,34,35] • Larotrectinib (if *NTRK* gene fusion-positive)[q,34,36] • Selpercatinib (if *RET* gene fusion-positive)[r,37]

[m] Pembrolizumab can be considered for patients with MSI-H, dMMR, or advanced TMB-H tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.
[o] There are no comparative data to define optimal treatment after first-line systemic therapy.
[p] Dabrafenib + trametinib can be considered for patients with *BRAF* V600E mutation-positive tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.
[q] Entrectinib and larotrectinib can be considered for patients with *NTRK* gene fusion-positive tumors without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments or that have progressed following treatment.
[r] Selpercatinib can be considered for patients with *RET* gene fusion-positive tumors that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

37 Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): A phase 1/2, open-label, basket trial. Lancet Oncol 2022;23:1261-1273

National Comprehensive Cancer Network (NCCN), 2023 [6]

Pancreatic Adenocarcinoma

Zielsetzung/Fragestellung

In the NCCN Guidelines for Pancreatic Adenocarcinoma, the diagnosis and management of adenocarcinomas of the exocrine pancreas are discussed; neuroendocrine tumors are not included.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

Version 1.2024 der Leitlinie, Erstveröffentlichung unklar.

- Repräsentatives Gremium mit Patientenvertretung;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt (NCCN Guidelines Panel Disclosures);
- Systematische Suche wird erwähnt, jedoch keine detaillierte Beschreibung und Suchzeitraum, keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren sind nicht näher beschrieben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist zudem über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Es wurde kein Suchzeitraum für die Literaturrecherche angegeben
- PubMed database

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet ('Discussion update in progress').

Empfehlungen

PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS 0–1	• FOLFIRINOX or modified FOLFIRINOX[d,e,5] • Gemcitabine + albumin-bound paclitaxel[d,6] • Liposomal irinotecan + 5-FU + leucovorin + oxaliplatin (NALIRIFOX)[i,16] Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX or modified FOLFIRINOX[d,e,5] • Gemcitabine + cisplatin[7,8]	• Gemcitabine • Gemcitabine + capecitabine[9] • Gemcitabine + erlotinib[f,10] • Capecitabine (category 2B) • Fluoropyrimidine + oxaliplatin ‣ Capecitabine + oxaliplatin (CapeOx)[11] (category 2B) ‣ 5-FU + leucovorin + oxaliplatin (OFF)[12] (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine + albumin-bound paclitaxel + cisplatin[13,14] (category 2B) • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX)[15] (category 2B)	• Induction chemotherapy with any of the preferred/other regimens (≥4 to 6 cycles) followed by chemoradiation[b,g] or SBRT[17] in selected patients (locally advanced disease without systemic metastases)[18] • Chemoradiation[b,h] or SBRT[h] (in patients who are not candidates for induction chemotherapy) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Pembrolizumab[j,21] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive)

Subsequent Therapy on PANC-F (8 & 9 of 12)

[b] Chemoradiation (PANC-F 10 of 12).
[d] The recommendations for FOLFIRINOX or modified FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.
[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[f] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[g] Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy.[16]
[h] If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation or SBRT. See Principles of Radiation Therapy (PANC-G).
[i] While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound paclitaxel, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX and adds considerably more expense compared to FOLFIRINOX.
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Intermediate PS 2	• Capecitabine • Gemcitabine • Gemcitabine + albumin-bound paclitaxel	• None	• Induction chemotherapy with any of the preferred regimens (≥4 to 6 cycles) followed by chemoradiation[b,g] or SBRT[17] in selected patients (locally advanced disease without systemic metastases) • Chemoradiation[b,h] or SBRT[h] (in patients who are not candidates for induction chemotherapy) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Pembrolizumab[j,21] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive)
Poor PS 3	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ‣ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ‣ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)	• None	• None

Subsequent Therapy on PANC-F (8 & 9 of 12)

[b] Chemoradiation (PANC-F 10 of 12).
[g] Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy.[16]
[h] If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation or SBRT. See Principles of Radiation Therapy (PANC-G).
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

Metastatic Disease (First-Line Therapy)

- Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS 0–1	• FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • NALIRIFOX[i,16] (category 1) • Gemcitabine + albumin-bound paclitaxel[6] (category 1) Only for known *BRCA1/2* or *PALB2* mutations: • FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • Gemcitabine + cisplatin[7,8]	• Gemcitabine (category 1) • Gemcitabine + erlotinib[f,10] (category 1) • Gemcitabine + capecitabine[9] • Gemcitabine + albumin-bound paclitaxel + cisplatin[13,14] • Fluoropyrimidine + oxaliplatin ‣ CapeOx[11] (category 2B) ‣ OFF[12] (category 2B) • GTX[15] (category 2B)	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Selpercatinib (if *RET* gene fusion-positive) • Pembrolizumab[j,21] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]

Maintenance Therapy for Metastatic Disease on PANC-F (7 of 12)
Subsequent Therapy on PANC-F (8 of 12)

[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[f] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[i] While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound paclitaxel, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX and adds considerably more expense compared to FOLFIRINOX.
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

References

Metastatic Disease (First-Line Therapy)

- Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Intermediate PS 2	• Gemcitabine + albumin-bound paclitaxel (category 1) • Capecitabine • Gemcitabine • If unable to tolerate FOLFIRINOX, consider: ‣ 5-FU + leucovorin + oxaliplatin (FOLFOX)[22,23] ‣ 5-FU + leucovorin + irinotecan (FOLFIRI)[24,25] ‣ CapeOx[26]	• None	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Pembrolizumab[j,21] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Selpercatinib (if *RET* gene fusion-positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]
Poor PS 3	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ‣ 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ‣ Fixed-dose-rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)	• None	• Pembrolizumab[j,21] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Larotrectinib (if *NTRK* gene fusion-positive) • Entrectinib (if *NTRK* gene fusion-positive) (category 2B) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]

Maintenance Therapy for Metastatic Disease on PANC-F (7 of 12)
Subsequent Therapy on PANC-F (8 & 9 of 12)

Metastatic Disease (Maintenance Therapy)

- Patients who have response or stable disease after 4–6 months of chemotherapy may undergo a chemotherapy holiday or maintenance therapy.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• If previous platinum-based chemotherapy: ‣ Olaparib (only for germline *BRCA1/2* mutations)	• Clinical trial or • If previous first-line FOLFIRINOX: ‣ Capecitabine or • If previous first-line gemcitabine + albumin-bound paclitaxel: ‣ Gemcitabine single agent (category 2B) ‣ Gemcitabine + albumin-bound paclitaxel modified schedule (category 2B)	• If previous first-line FOLFIRINOX: ‣ 5-FU + leucovorin[k,27] ‣ FOLFIRI[k,27] ‣ FOLFOX[l,27] (category 2B) • Prior platinum-based therapy ‣ Rucaparib (for germline or somatic *BRCA1/2* or *PALB2* mutations)[m,n,28]

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

	Preferred Regimens	Other Recommended Regimens		Useful in Certain Circumstances
Good PS 0–1	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) If no prior immunotherapy: • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb])	• Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Selpercatinib (if *RET* gene fusion-positive)[29] If no prior immunotherapy: • Dostarlimab-gxly[j] (if MSI-H or dMMR) • Nivolumab + ipilimumab[j] (if TMB-H [≥10 mut/Mb]) (category 2B) If prior gemcitabine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[30] (category 1 for metastatic disease) • Bolus 5-FU + leucovorin • Capecitabine • CapeOx • Continuous infusion 5-FU • FOLFIRI[31-33] • FOLFIRINOX or modified FOLFIRINOX[e,34] • FOLFOX • OFF	If prior fluoropyrimidine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[30] (if no prior irinotecan) • Gemcitabine • Gemcitabine + albumin-bound paclitaxel • Gemcitabine + cisplatin (only for known *BRCA1/2* or *PALB2* mutations) • Gemcitabine + erlotinib[f,35] • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] (category 2B)	• Adagrasib (if *KRAS G12C* mutation-positive) • Sotorasib (if *KRAS G12C* mutation-positive) • Chemoradiation,[b] if not previously given, only an option for: ‣ Locally advanced disease if primary site is the sole site of progression ‣ Select patients with recurrent disease in combination with systemic therapy

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Intermediate PS 2	• None	If prior fluoropyrimidine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[30] (if no prior irinotecan) • Gemcitabine + albumin-bound paclitaxel If prior gemcitabine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[30] (category 1 for metastatic disease)	• Adagrasib (if *KRAS G12C* mutation positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Sotorasib (if *KRAS G12C* mutation-positive) • Chemoradiation[b] if not previously given, only an option for: ‣ Locally advanced disease if primary site is the sole site of progression ‣ Selected patients with recurrent disease in combination with systemic therapy If no prior immunotherapy: • Dostarlimab-gxly[j] (if MSI-H or dMMR) • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Nivolumab + ipilimumab[j] (if TMB-H [≥10 mut/Mb]) (category 2B)
Poor PS 3	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) If no prior immunotherapy: • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Dostarlimab-gxly[j] (if MSI-H or dMMR) (category 2B)	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ‣ 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ‣ Fixed-dose-rate gemcitabine (10 mg/m^2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)	• Dabrafenib + trametinib (if *BRAF* V600E mutation positive)[19,20] • Adagrasib (if *KRAS G12C* mutation-positive) (category 2B) • Sotorasib (if *KRAS G12C* mutation-positive) (category 2B)

[b] Chemoradiation (PANC-F 10 of 12).
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

References

PRINCIPLES OF SYSTEMIC THERAPY

Chemoradiation

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Capecitabine + concurrent RT • Continuous infusion 5-FU + concurrent RT	• Gemcitabine + concurrent RT[36]	• None

*29 Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol 2022;23:1261-1273.

National Comprehensive Cancer Network (NCCN), 2024 [2]

Breast Cancer

Zielsetzung/Fragestellung

These NCCN Clinical Practice Guidelines for Breast Cancer include up-to-date guidelines for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget's disease, phyllodes tumor, inflammatory breast cancer, and breast cancer during pregnancy.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

Version 2.2024 der Leitlinie, Erstveröffentlichung unklar.

- Repräsentatives Gremium mit Patientenvertretung;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt (NCCN Guidelines Panel Disclosures);
- Systematische Suche wird erwähnt, jedoch keine detaillierte Beschreibung und Suchzeitraum, keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren sind nicht näher beschrieben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist zudem über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Es wurde kein Suchzeitraum für die Literaturrecherche angegeben
- PubMed database

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet ('Discussion update in progress').

Empfehlungen

TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[w]	*PIK3CA* activating mutation	NGS, PCR (Blood or tumor tissue if blood negative)	Alpelisib + fulvestrant[x]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative[y]	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, (Blood or tumor tissue if blood negative)	Capivasertib + fulvestrant[y]	Category 1	Preferred second- or subsequent-line therapy in select patients[y]
HR-positive/ HER2-negative[z]	*ESR1* mutation	NGS, PCR (Tumor tissue or blood)	Elacestrant[z]	Category 2A	Other recommended regimen
Any	Germline *BRCA1* or *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (Tumor tissue or blood)	Larotrectinib[aa] Entrectinib[aa]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR, (Tumor tissue)	Pembrolizumab[bb,cc] Dostarlimab-gxly[dd]	Category 2A	
Any	TMB-H (≥10 mut/Mb)	NGS (Tumor tissue or blood)	Pembrolizumab[bb,cc]	Category 2A	
Any	*RET*-fusion	NGS (Tumor tissue or blood)	Selpercatinib[ee]	Category 2A	

[w] For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

[x] The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

[y] In adult patients with *PIK3CA* or *AKT1* activating mutations, or for *PTEN* alterations after disease progression or recurrence after ≥1 prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

[z] For postmenopausal or premenopausal patients receiving ovarian ablation or suppression or adult males with ER-positive, HER2-negative, *ESR1*-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor. Assess for ESR1 mutations at progression following prior lines of endocrine therapy.

[aa] Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an NTRK gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment.

[bb] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[cc] Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, or TMB-H tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

[dd] Dostarlimab-gxly is indicated for adult patients with MSI-H/dMMR unresectable or metastatic tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

[ee] Selpercatinib is indicated for adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

National Comprehensive Cancer Network (NCCN), 2024 [5]

Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Zielsetzung/Fragestellung

These NCCN Guidelines for Ovarian Cancer discuss cancers originating in the ovary, fallopian tube, or peritoneum and include recommendations for epithelial subtypes, including serous, endometrioid, carcinosarcoma (malignant mixed Müllerian tumors [MMMTs] of the ovary), clear cell, mucinous, and borderline epithelial tumors (also known as low malignant potential [LMP] tumors). The recommendations are primarily based on data from patients with the most common subtypes—high-grade serous and grade 2 and 3 endometrioid carcinoma. Also included in the guidelines are recommendations for less common ovarian cancers (LCOC), specifically carcinosarcoma, clear cell carcinoma, mucinous carcinoma, low-grade serous carcinoma, grade 1 endometrioid carcinoma, borderline epithelial tumors, and non-epithelial subtypes including malignant sex cord-stromal tumors and germ cell tumors.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

Version 1.2024 der Leitlinie, Erstveröffentlichung unklar.

- Repräsentatives Gremium mit Patientenvertretung;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt (NCCN Guidelines Panel Disclosures);
- Systematische Suche wird erwähnt, jedoch keine detaillierte Beschreibung und Suchzeitraum, keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren sind nicht näher beschrieben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist zudem über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Es wurde kein Suchzeitraum für die Literaturrecherche angegeben
- PubMed database

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet ('Discussion update in progress').

Empfehlungen

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Sensitive Disease[r] (alphabetical order)

Preferred Regimens	Other Recommended Regimens[u]	Useful in Certain Circumstances
Carboplatin/ gemcitabine[14] ± bevacizumab[k,s,t,15] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19] Cisplatin/gemcitabine[20] Targeted Therapy (single agents) Bevacizumab[k,s,21,22]	Capecitabine Carboplatin[14] Carboplatin/docetaxel[23, 24] Carboplatin/paclitaxel (weekly)[g,25] Cisplatin[18] Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine Targeted Therapy Niraparib/bevacizumab (category 2B)[k,26] Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	For mucinous carcinoma: • 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[k,s] • Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[k,s] Carboplatin/paclitaxel (for age >70)[g,y] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity) Irinotecan/cisplatin (for clear cell carcinoma)[31] Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[z] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors) (category 2B)[k,33] Selpercatinib (for *RET* gene fusion-positive tumors)[z,34] For low-grade serous carcinoma: • Trametinib[35] • Binimetinib (category 2B)[36,37] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,38] Pembrolizumab (for MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥10 mutations/megabase)[z,39]

[g] Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.
[j] Tamoxifen is not recommended for low-grade serous carcinoma.
[k] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[p] Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[q] Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy (Griffiths RW, et al. Int J Gyn Ca 2011;21:58-65). Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.
[r] In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[s] Contraindicated for patients at increased risk of GI perforation.
[t] If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity. Discontinue bevacizumab before initiating maintenance therapy with a PARPi.
[u] Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.
[v] For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.
[w] For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[x] For patients with deleterious germline and/or somatic *BRCA* mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[y] For recommended dosing for individuals >70 years, see OV-C, 7 of 12.
[z] Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF*, FRα (FOLR1), *RET*, and *NTRK* if prior testing did not include these markers. More comprehensive testing may be particularly important in LCOC with limited approved therapeutic options (OV-B).

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[k,40] Docetaxel[41] Etoposide (oral)[42] Gemcitabine[43,44] Liposomal doxorubicin[43,44] Liposomal doxorubicin/ bevacizumab[k,s,45] Paclitaxel (weekly)[g,46] Paclitaxel (weekly)/ bevacizumab[g,k,s,45] Topotecan[47,48] Topotecan/bevacizumab[k,s,45] Targeted Therapy (single agents) Bevacizumab[k,s,21,22] Mirvetuximab soravtansine-gynx (for FRα-expressing tumors)[z,49]	Cytotoxic Therapy[u] Capecitabine Carboplatin* Carboplatin/docetaxel* Carboplatin/paclitaxel (weekly)[g,*] Carboplatin/gemcitabine[14] ± bevacizumab[k,s,t,15,*] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17,*] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19,*] Cyclophosphamide Cyclophosphamide (oral)/pembrolizumab/bevacizumab[k,51,52] Doxorubicin Gemcitabine/bevacizumab[k,53] Gemcitabine/cisplatin[20,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[k,aa,54] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[50] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	Carboplatin/paclitaxel (for age >70)[g,y,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)* Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,38] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/ megabase)[z,39] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[z] Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+])[55] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors)[k,z,33,56,57] Selpercatinib (for *RET* gene fusion-positive tumors)[z,34] For low-grade serous carcinoma: • Trametinib[35] • Binimetinib (category 2B)[36,37]

* Platinum agents have limited activity when the disease has demonstrated growth through a platinum-based regimen, and platinum rechallenge is generally not recommended in this setting.

Footnotes

National Comprehensive Cancer Network (NCCN), 2024 [3]

Colon Cancer

Zielsetzung/Fragestellung

These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist, and address diagnosis, pathologic staging, surgical management, perioperative treatment, surveillance, management of recurrent and metastatic disease, and survivorship.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

Version 1.2024 der Leitlinie, Erstveröffentlichung unklar.

- Repräsentatives Gremium mit Patientenvertretung;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt (NCCN Guidelines Panel Disclosures);
- Systematische Suche wird erwähnt, jedoch keine detaillierte Beschreibung und Suchzeitraum, keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren sind nicht näher beschrieben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist zudem über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Es wurde kein Suchzeitraum für die Literaturrecherche angegeben
- PubMed database

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet ('Discussion update in progress').

Empfehlungen

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,o]
pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

SECOND-LINE AND SUBSEQUENT THERAPY OPTIONS (if not previously given)[c,p]		
Previous oxaliplatin-based therapy without irinotecan	**Previous therapy with oxaliplatin and irinotecan**	**Biomarker-directed therapy**
• FOLFIRI[i] or irinotecan[i] • FOLFIRI[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFIRI[i] + (cetuximab or panitumumab)[f,s] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[h]: ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ‣ Fruquintinib ‣ Regorafenib ‣ Trifluridine + tipiracil ± bevacizumab[e] (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[f] ‣ Encorafenib + (cetuximab or panitumumab)[t] • HER2-amplified and *RAS* and *BRAF* WT[f] ‣ (Trastuzumab[l] + [pertuzumab or lapatinib or tucatinib])[m] • HER2-amplified ‣ Fam-trastuzumab deruxtecan-nxki[u] • *KRAS* G12C mutation positive[f] ‣ (Sotorasib or adagrasib)[v] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ‣ Entrectinib or larotrectinib • *RET* gene fusion-positive ‣ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	**Previous therapy without oxaliplatin or irinotecan**	
• FOLFOX[d] or CAPEOX[d] • FOLFOX[d] + bevacizumab[e] • CAPEOX[d] + bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFOX[d] + (cetuximab or panitumumab)[f] ‣ CAPEOX[d] + (cetuximab or panitumumab)[f] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[d] or CAPEOX[d] • (FOLFOX or CAPEOX)[d] + bevacizumab[e] • FOLFIRI[i] or irinotecan[i] • (FOLFIRI or irinotecan)[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + oxaliplatin[d] ± bevacizumab[e] • FOLFIRINOX[d,k] ± bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFIRI[h] + (cetuximab or panitumumab)[f,s] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	

Hintergrund

Selpercatinib for RET Gene Fusion-Positive Disease in the Non-First- Line Setting In the ongoing phase 1/2 LIBRETTO-001 trial, the efficacy and safety of the highly selective RET kinase inhibitor selpercatinib is being investigated in a diverse group of patients with RET gene fusion-positive tumors, including 10 patients with colon cancer.[725] Patients in this trial had received a median of 2 prior lines of systemic therapy and 31% of patients received 3 or more prior lines of treatment. Of a total of 41 efficacy evaluable patients, the ORR for the entire cohort by independent review was 43.9% (95% CI, 28.5–60.3) and 20% in the colon cancer subgroup (95% CI, 2.5–55.6). There were 2 complete responses (5%), although neither patient had colon cancer. For the entire cohort, median PFS was 13.2 months (95% CI, 7.4–26.2) by independent review, median OS was 18 months (95% CI, 10.7–not evaluable), and median duration of response was 24.5 months (95% CI, 9.2–not evaluable). For the colon cancer subgroup, median duration of response was 9.4 months (95% CI, 5.6–13.3). The most common grade 3 or higher treatment emergent AEs were hypertension and transaminitis. The most common treatment-related serious AEs were drug-induced livery injury, fatigue, and hypersensitivity. One patient had to permanently discontinue selpercatinib due to drug induced liver injury. Based on these data, the FDA has approved selpercatinib for locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.[965]

Referenzen

725. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, openlabel, basket trial. Lancet Oncol 2022;23:1261-1273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36108661

965. U.S. Food & Drug Administration. Package Insert. selpercatinib capsules, for oral use. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213246s008l bl.pdf. Accessed February 13, 2023.

National Comprehensive Cancer Network (NCCN), 2024 [7]

Rectal Cancer

Zielsetzung/Fragestellung

These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, management of recurrent and metastatic disease, patient surveillance, and survivorship. These guidelines overlap considerably with the NCCN Guidelines® for Colon Cancer, especially in the treatment of metastatic disease.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

Version 1.2024 der Leitlinie, Erstveröffentlichung unklar.

- Repräsentatives Gremium mit Patientenvertretung;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt (NCCN Guidelines Panel Disclosures);
- Systematische Suche wird erwähnt, jedoch keine detaillierte Beschreibung und Suchzeitraum, keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren sind nicht näher beschrieben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist zudem über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Es wurde kein Suchzeitraum für die Literaturrecherche angegeben
- PubMed database

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet ('Discussion update in progress').

Empfehlungen

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,n]
pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

SECOND-LINE AND SUBSEQUENT THERAPY OPTIONS (if not previously given)[c,o]		
Previous oxaliplatin-based therapy without irinotecan	**Previous therapy with oxaliplatin and irinotecan**	**Biomarker-directed therapy**
• FOLFIRI[h] or irinotecan[h] • FOLFIRI[h] + (bevacizumab[e,p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q]) • Irinotecan[h] + (bevacizumab[e,p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q]) • If *KRAS/NRAS/BRAF* WT[g]: ▸ FOLFIRI[h] + (cetuximab or panitumumab)[f,r] ▸ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[g]: ▸ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ▸ Fruquintinib ▸ Regorafenib ▸ Trifluridine + tipiracil ± bevacizumab[e] (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[f] ▸ Encorafenib + (cetuximab or panitumumab)[s] • HER2-amplified and *RAS* and *BRAF* WT[f] ▸ (Trastuzumab[k] + [pertuzumab or lapatinib or tucatinib])[l] • HER2-amplified ▸ Fam-trastuzumab deruxtecan-nxki[t] • *KRAS* G12C mutation positive[f] ▸ (Sotorasib or adagrasib)[u] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ▸ Entrectinib or larotrectinib • *RET* gene fusion-positive ▸ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	**Previous therapy without oxaliplatin or irinotecan**	
• FOLFOX[d] or CAPEOX[d] • FOLFOX[d] + bevacizumab[e] • CAPEOX[d] + bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[g]: ▸ FOLFOX[d] + (cetuximab or panitumumab)[f] ▸ CAPEOX[d] + (cetuximab or panitumumab)[f] ▸ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[d] or CAPEOX[d] • (FOLFOX or CAPEOX)[d] + bevacizumab[e] • FOLFIRI[h] or irinotecan[h] • (FOLFIRI or irinotecan)[h] + (bevacizumab[e,p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q]) • Irinotecan[h] + oxaliplatin[d] ± bevacizumab[e] • FOLFIRINOX[d,j] ± bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[g]: ▸ FOLFIRI[h] + (cetuximab or panitumumab)[f,r] ▸ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy)	

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2024) am 15.04.2024

#	Suchfrage
1	MeSH descriptor: [Proto-Oncogene Proteins c-ret] explode all trees
2	(RET OR (RET NEXT PTC*) OR RET9 OR RET51 OR MEN2A OR MEN2B OR "rearranged during transfection"):ti,ab,kw
3	MeSH descriptor: [Neoplasms] explode all trees
4	(cancer* OR tumor* OR tumour* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
5	#2 AND (#3 OR #4)
6	(solid NEAR/2 (tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR neoplas* OR sarcoma* OR cancer* OR lesion* OR malignan*)):ti,ab,kw
7	((agnostic OR independent) AND (tumor* OR tumour* OR tissue OR histology)):ti
8	#1 OR #5 OR #6 OR #7
9	#8 with Cochrane Library publication date from Apr 2019 to present

Systematic Reviews in PubMed am 15.04.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"Proto-Oncogene Proteins c-ret"[mh]
2	ret protein, human[nm]
3	RET[tiab] OR RET-PTC*[tiab] OR RET9[tiab] OR RET51[tiab] OR MEN2A[tiab] OR MEN2B[tiab] OR rearranged during transfection[tiab]
4	neoplasms[mh]
5	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab]
6	#3 AND (#4 OR #5)
7	solid[ti] AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR sarcoma*[ti] OR cancer*[ti] OR lesion*[ti] OR malignan*[ti])
8	(agnostic[ti] OR independent[ti]) AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR tissue[ti] OR histology[ti])
9	#1 OR #2 OR #6 OR #7 OR #8
10	(#9) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR

#	Suchfrage
	meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
11	(#10) AND ("2019/04/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT "The Cochrane database of systematic reviews"[Journal]
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 15.04.2024

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"Proto-Oncogene Proteins c-ret"[mh]
2	ret protein, human[nm]
3	RET[tiab] OR RET-PTC*[tiab] OR RET9[tiab] OR RET51[tiab] OR MEN2A[tiab] OR MEN2B[tiab] OR rearranged during transfection[tiab]
4	neoplasms[mh]
5	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab]
6	#3 AND (#4 OR #5)
7	"solid tumor"[tiab:~2] OR "solid tumors"[tiab:~2] OR "solid tumour"[tiab:~2] OR "solid tumours"[tiab:~2] OR "solid neoplasm"[tiab:~2] OR "solid neoplasms"[tiab:~2] OR "solid cancer"[tiab:~2] OR "solid cancers"[tiab:~2] OR

#	Suchfrage
	"solid carcinoma"[tiab:~2] OR "solid carcinomas"[tiab:~2] OR "solid malignancy"[tiab:~2] OR "solid malignancies"[tiab:~2]
8	(agnostic[ti] OR independent[ti]) AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR tissue[ti] OR histology[ti])
9	#1 OR #2 OR #6 OR #7 OR #8
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
11	(#10) AND ("2019/04/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur zu RET-Fusions-positiven soliden Tumoren, abgeschlossen am 17.04.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Iterative Handsuche nach grauer Literatur zu Ovarialkarzinom, Pankreaskarzinom, Kolorektalkarzinom, Mammakarzinom, Speicheldrüsenkarzinom, Neuroendokrine Tumore sowie Krebserkrankung mit unbekanntem Primärtumor, abgeschlossen am 23.04.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)

- National Institute for Health and Care Excellence (NICE)
- Alberta Health Service (AHS)
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

Referenzen

1. **Li AY, McCusker MG, Russo A, Scilla KA, Gittens A, Arensmeyer K, et al.** RET fusions in solid tumors. Cancer Treat Rev 2019;81:101911.
2. **National Comprehensive Cancer Network (NCCN).** Breast cancer, Version 2.2024 [online]. Plymouth Meeting (USA): NCCN; 2024. [Zugriff: 17.04.2024]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
3. **National Comprehensive Cancer Network (NCCN).** Colon cancer, Version 1.2024 [online]. Plymouth Meeting (USA): NCCN; 2024. [Zugriff: 17.04.2024]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
4. **National Comprehensive Cancer Network (NCCN).** Neuroendocrine and adrenal tumors, Version 1.2023 [online]. Plymouth Meeting (USA): NCCN; 2023. [Zugriff: 17.04.2024]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
5. **National Comprehensive Cancer Network (NCCN).** Ovarian cancer including fallopian tube cancer and primary peritoneal cancer, Version 1.2024 [online]. Plymouth Meeting (USA): NCCN; 2024. [Zugriff: 17.04.2024]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
6. **National Comprehensive Cancer Network (NCCN).** Pancreatic adenocarcinoma, Version 1.2024 [online]. Plymouth Meeting (USA): NCCN; 2023. [Zugriff: 17.04.2024]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
7. **National Comprehensive Cancer Network (NCCN).** Rectal cancer, Version 1.2024 [online]. Plymouth Meeting (USA): NCCN; 2024. [Zugriff: 17.04.2024]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf.
8. **Parimi V, Tolba K, Danziger N, Kuang Z, Sun D, Lin DI, et al.** Genomic landscape of 891 RET fusions detected across diverse solid tumor types. NPJ Precis Oncol 2023;7(1):10.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO